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SYPHILIS IN THE ÆTIOLOGY AND DIAGNOSIS OF TUBERCULOSIS *

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THE confusion between syphilis and tuberculosis must have been a sore trial to the early morbid anatomists, and even to the clinicians. Some of the older writers believed that syphilis tended to protect a patient against tuberculosis, others that it predisposed him to infection. The more precise methods of laboratory diagnosis have, it is true, produced in recent years a wealth of new material, but they have by no means settled for us this vexed question. Rather they appear to have complicated certain aspects of it, as, for example, the interpretation of the Wassermann reaction in tuberculosis. Before attempting to draw any conclusions, therefore, it is essential to collect and examine the data.

ÆTIOLOGY

Beginning with the question of ætiology, two main issues are involved in the inquiry: (1) the possibility of syphilis preparing the soil for the seed of tuberculosis and (2) the effect of intercurrent syphilis upon an active or quiescent tuberculosis. Except, however, in the case of tuberculous patients who actually develop a chancre and signs of secondary syphilis during the period of observation, and in the case of childhood tuberculosis with a syphilitic heredity, it is often impossible to decide which is the antecedent disease. It will be therefore best to record first those cases which show evidence of both diseases irrespective of priority. Let us take first the record of positive Wassermann reactions in tuberculosis institutions and in tuberculous patients generally.

Hollander and F. C. Narr¹ have analysed the published records of different observers. These records show

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a definitely positive Wassermann reaction in 10.36 per cent. of 6,324 tuberculous persons. The highest record in the series is that of Letulle and his colleagues, which deals with French patients. Their proportion of positives is 19 per cent. The remainder of the records in the series is American, and the figures range from 2 to 17 per cent. of positives. It would be easy to add still more records to this list. Two, however, will suffice. The first is that of Adelung,² of America, which I quote because all his patients were pulmonary cases with tubercle bacilli in the sputum. He found 8.7 per cent. of positive Wassermann reactions in 195 patients. The second, quoted because it is the only one I can find concerning Great Britain, is that of Bowman.³ Examining 500 patients in the Glasgow City Sanatorium, he found 9.42 per cent. of positives in 223 pulmonary cases and 5.05 per cent. in 277 non-pulmonary cases. As a rough control of all these figures may be quoted Kilduffe's series⁴ of 12 per cent. of positives in 484 unselected patients attending a general hospital in Pittsburg, where presumably patients of different European and American stocks are represented. This figure is slightly higher than that given (8-10 per cent.) by the Royal Commission on Venereal Diseases in this country in 1916.

Obviously, it is not possible to make a very strict comparison between these figures, which are compiled from different types of clinical materials and from different sources. For instance, many of them are crude figures, including acquired and hereditary syphilis. Those interested in this subject are referred to a very thorough paper by Ritter,⁵ in which a large collection of data from more than fifty sources is given.

At Victoria Park it is not our practice to make a Wassermann test on all patients. On looking up the records I find that tests have been carried out on 137 patients from the tuberculosis and observation wards during the last four years. Of these twenty-six (19 per cent.) were positive, but only six of them (4 per cent. of the total) showed definite and conclusive evidence of tuberculosis, the others being probably, if not certainly, non-tuberculous. Of these six one was a fatal case of pulmonary tuberculosis and another a fatal case of tuberculous peritonitis in a child; the other four were males with the chronic middle-aged type of pulmonary

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tuberculosis, one having a tuberculous larynx and another *tabes dorsalis*. Obviously, some selection was at work in having Wassermann tests done on these cases, but, whatever their interpretation, they do not emphasise syphilis as a predisposing cause of tuberculosis. To sum up, the figures from various sources quoted above show that the percentage of positive Wassermann reactions in institutions dealing with cases of tuberculosis and with tuberculous patients generally is, broadly speaking, little higher than that found in the general population.

The next question which arises is, Do phthisis cases with a syphilitic history exhibit a form of tuberculosis differing from that usually found in non-specific patients? Some writers⁶ have described a caseous pneumonic type of tuberculosis and a liability to early lardaceous disease; Sergeant,⁷ a fibroid form of pulmonary tuberculosis of slow growth and associated with emphysema and arteriosclerosis; Morton,⁸ again, an increased liability to laryngeal tuberculosis. My experience at Victoria Park leads me to agree in general with the last two-named views, but not with the first. I have not seen the caseous pneumonic type associated with syphilis, and in any case this type of pulmonary tuberculosis in adults is becoming rarer.

Now let us approach the question from the opposite angle. What percentage of known syphilitics develop tuberculosis? The high figures sometimes quoted from Bronfenbrenner (43 per cent.) and Tedeschi (70 per cent.) are open to various interpretations, and it is safer to quote more recent sets. Samson⁹ examined a group of 1,300 prostitutes in Berlin and found amongst the Wassermann-positive cases 12·5 per cent. of cases with active tuberculosis, and amongst the Wassermann-negative cases 10·7 per cent. Elliott¹⁰ has put the figure lower, viz., 3 to 5 per cent. of tuberculous patients amongst the syphilitics attending the University Hospital, Michigan.

With regard to tuberculosis as a terminal complication of late syphilitic and parasyphilitic diseases the evidence is conflicting. Osler,¹¹ on the authority of Stokes, stated that tuberculosis was not uncommon in aneurysm, but in the last 53 cases of thoracic aneurysm examined post mortem at Victoria Park, it has been found only twice, a rarity comparable with the association of valvular disease and tuberculosis. Mott¹² stated that recent active

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tuberculosis was commonly found in autopsies on general paralytics, especially females, but it appears to be fairly common also in dementia præcox and in acute maniacal and melancholic states, which are non-specific, whilst it is uncommon in tabes. It would be unjustifiable, therefore, to attribute terminal tuberculosis to the syphilitic taint.

There is, however, one small but important group of cases exhibiting the coincidence of syphilis and tuberculosis in which the evidence of the effect of one disease upon the other seems indisputable, viz., the relatively rare cases in which a patient with active phthisis acquires syphilis. Here all writers seem to be agreed that the secondary syphilis, with its accompanying systemic disturbance, exercises a definitely bad effect on the active tuberculous lesion.

Records of post-mortem examinations frequently do not refer to the association of these two diseases. Landsberger¹³ published a series of 5,332 autopsy records in which syphilis and florid tuberculosis were associated in 0.77 per cent. of cases and syphilis and healed tuberculosis in 0.99 per cent.

Finally, there remains the question of inherited syphilis and tuberculosis. Here, on the one hand, we have the statement of Caronia and Marinucci¹⁴ that a series of 70 children in Naples with bone and joint tuberculosis revealed an incidence of 72.3 per cent. inherited syphilis, and another Italian record by de Angelis¹⁵ to the effect that tuberculin and Wassermann tests on children in an orphanage gave in one group a percentage of double infection as high as 48.5. Hutinel and Merklen¹⁶ also comment on the existence of inherited syphilis in tuberculous meningitis (11 out of 206). In this country, Munro,¹⁶ in a careful piece of work, recorded 11 per cent. of inherited syphilis cases in tuberculous children in Fife and Kinross Sanatorium. These cases, all of whom had a positive Wassermann reaction, showed in all but one instance other stigmata of hereditary syphilis. With regard to their tuberculous disease, either glandular or pulmonary lesions or both were present in all cases but one, which was a case of spinal disease. Taking the incidence of hereditary syphilis in a general child population as being something under 10 per cent., Munro¹⁷ considers from a study of his own

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cases that syphilis as predisposing to a subsequent tuberculous infection is not proven.

What conclusions, therefore, can we draw from all these records, many of them divergent? Obviously, they must be very tentative.

- (1) It is reasonable to suppose that the malnutrition so often accompanying inherited syphilis may offer a suitable soil for the tubercle bacillus, but there are many difficulties in proving the point.
- (2) Clinicians appear to be agreed that syphilis acquired during the active stage of pulmonary tuberculosis exercises a bad effect on the tuberculosis.
- (3) In the later stages of syphilis ulcerating surfaces may, as pointed out by Sergeant, offer a suitable point of entrance for the tubercle bacillus. Possibly an example of this effect may be seen in some cases of laryngeal tuberculosis.
- (4) The diffuse so-called syphilitic fibrosis probably does not render a patient more liable to tuberculosis. It may indeed protect him, since the tubercle bacillus does not readily attack fibrous tissue.
- (5) When large numbers of cases, including both latent and active, are analysed, the predisposing effect of the one disease upon the other is not well marked.

THE EXPERIMENTAL EVIDENCE

The spirochæte does not lend itself readily to laboratory experiments, especially in animals. It is strictly anaerobic, whereas the tubercle bacillus is equally obstinately aerobic.

As regards symbiosis little is known. A few cases have been recorded in which both parasites have been found together in the lymph nodes of man. W. and R. Spitzer¹⁸ examined three such cases, two of fistulous cervical adenitis, the third of caseous epitrochlear nodes with a generalised papular syphilide. Spirochætes were found in all three cases, and all three glands produced generalised tuberculosis when inoculated into guinea-pigs.

The same workers have attempted to graft syphilitic infection on to rabbits previously injected with bovine

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tubercle bacilli, and *vice versâ*, but without any apparent influence upon the course of either disease. Unfortunately, the strain of bovine tubercle bacillus used was found to be of low virulence.

Numerous allergy experiments have also been made, but they are not very convincing, and the attempt to separate tuberculosis into three stages, primary, secondary and tertiary, like syphilis, is rather arbitrary. Most of the work (Dujardin and Duprez¹⁹) on allergy has been done with skin tests, using leutin and tuberculin as the two antigens, but this method is by no means free from error. Perhaps the most interesting result (Lelong and Rivalier²⁰) is that of a positive tuberculin reaction diminishing in intensity with the onset of secondary syphilis.

Further animal experiments are needed, but they are obviously difficult to make, owing to the refractory character of the spirochæte.

DIAGNOSIS

First, as to serological methods. The Wassermann test is now so well established that a discussion on it is unnecessary here. The chief difficulty is the point raised by some workers as to the possibility of non-specific cross fixation. This question has been investigated by several workers. Dulaney²¹ made a careful test of 600 sera, 100 being sera of tuberculous patients and 500 of routine blood samples sent for Wassermann tests. Eight of the 100 sera from tuberculous patients gave a positive Wassermann with cholesterolised antigen, but this proportion is not notably higher than results obtained by other workers with non-cholesterolised antigen. In the group of 500 routine Wassermann sera, 15 from patients who had no signs of tuberculosis gave positive fixations with both tuberculosis and Wassermann antigens, *i.e.*, 3 per cent. These results appear to me to be more striking than those in the first group, but it must be remembered that active tuberculosis is sometimes difficult to diagnose clinically, and that a positive complement-fixation test without clinical signs is not necessarily incorrect. The conclusion appears to be that (1) positive Wassermann tests occurring in known tuberculous patients should be repeated with both cholesterolised and non-cholesterolised anti-

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gens ; (2) positive complement-fixation tests in syphilitics should be accepted with reserve. If I may record with own experience, I had encountered no difficulty my cholesterolised antigen until we came to investigate, at Victoria Park, a special group of mal-nourished so-called "pre-tuberculous" children. Here the question of inherited syphilis arises in a particularly difficult form, and the cases are being tested with both cholesterolised and non-cholesterolised antigens. This investigation is still going on. I have no conclusions to offer as yet, but I am beginning to doubt if the presence of cholesterol is a serious drawback.

The differential diagnosis in tissues may offer considerable difficulties. A few cases have been recorded in which both *Tr. pallidum* and *B. tuberculosis* have been found in the same lymph gland. Similarly, Sergeant states that *B. tuberculosis* has been found on primary sores, but if so, such a happening must be extremely rare, and one would always be afraid that confusion with the smegma bacillus had occurred unless an animal inoculation test had been made.

In cases in which it is not possible to make a Wassermann test reliance must be placed on other diagnostic distinctions. It is noteworthy that syphilis tends to affect the cardio-vascular system whilst tuberculosis does not. Syphilitic lesions of the liver are common ; in tuberculosis lesions in the liver are rare. On the other hand, the tubercle bacillus readily finds its nidus in the lung, where the spirochæte is only very rarely found. Enlargement of lymph glands, with frequent caseation, fills the picture much more in tuberculosis than in syphilis, where breaking down is rare. These differences could be multiplied to a considerable extent. It would appear, indeed, that there is a deep underlying difference between the cellular responses of the tissues to these two parasites, the one a bacterium, the other a protozoon, and we see this difference still further stressed in the effect of antiseptics and chemotherapeutic remedies on the two parasites. In morbid histology the real difficulty is likely to arise in the case of small gummata. The prominence of new-formed vessels with scanty formation of epithelioid and giant cells in syphilis, and the presence of avascular caseation with giant cells, many epithelioid cells and even tubercle bacilli in tuberculosis are the chief points of distinction.

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Too much stress cannot be laid on the finding of the tubercle bacillus. It is all-important. Ziehl Neelsen stained sections are a necessity. In other words, histology is of vital importance in tuberculosis, but of secondary importance in syphilis.

Syphilis of the lung offers special difficulties. Three forms have been described : (1) bronchitis during secondary syphilis ; (2) gummata, and (3) diffuse pulmonary fibrosis in the tertiary. The first mentioned offers little difficulty. Gummata of the lung I have not seen in seventeen years' experience of post-mortem work at Victoria Park. Pulmonary fibrosis with a positive Wassermann is not very uncommon, but, in the absence of other signs of syphilis, it is by no means certain that the fibrosis can be regarded as of specific origin, since fibrosis of lung without syphilis is a fairly common disease. In doubtful cases the sputum should be examined for tubercle bacilli daily for at least a week before being passed as negative, and in children the fæces should also be examined for tubercle bacilli. In passing it may be noted that in a recent series of cases I have found mouth spirochætes in 10 per cent. of sputa sent for routine examination for tubercle bacilli. Broncho-pulmonary spirochætosis, a disease in which hæmoptysis is a prominent symptom, seems to be a separate entity and has probably no relation either to syphilis or tuberculosis. The so-called lymphosarcomata appear occasionally to have been regarded as gummata. It must always be borne in mind that a positive Wassermann reaction may occur with either malignant disease or tuberculosis of the lung. Gummata of the sternum may complicate the diagnosis occasionally.

The examination of the cerebrospinal fluid for the purpose of differentiating between tuberculous meningitis and syphilis of the central nervous system can only be mentioned briefly in passing. As a general rule, the tubercle bacillus can be found in the fine skein of clot which forms in the fluid soon after withdrawal, whilst the Wassermann reaction is positive in the syphilitic cases either in the blood or cerebrospinal fluid. The cell count, globulin and protein estimations, and the colloidal gold tests are subsidiary tests which need not be dealt with in detail. They are chiefly important in supporting the Wassermann test.

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Perhaps one of the most difficult groups of cases in which to distinguish syphilis from tuberculosis is the surgical tuberculosis group of bone and joint diseases, especially when there is no discharging sinus from which to obtain pus for examination. A positive Wassermann does not necessarily exclude tuberculosis, and when possible, any tissue available should be submitted to histological examination. The same remark applies to cutaneous tuberculosis, especially in Bazin's disease.

Finally, there are the questions of the interpretation of the complement-fixation test in tuberculosis and of the various flocculation and precipitation tests in both diseases. The value of the complement-fixation test depends largely on the choice of antigen. For my own part, I much prefer the use of antigens consisting of tubercle bacilli suspended in saline rather than those made from liquid cultures containing egg, etc. Difficulties of cross-fixation arise here, as in the case of the Wassermann test, since tubercle bacilli possess a considerable amount of lipoid substances. On the whole it seems safe to regard a definitely positive reaction as indicating active tuberculosis, but it is by no means clear how a weak positive result should be interpreted, especially if the patient should happen to give a positive Wassermann. In all cases a graduated series of dilutions of serum should be used, as in making Wassermann tests on cerebrospinal fluid.

A large number of precipitation and flocculation tests have been devised both for tuberculosis and for syphilis. I have no experience of them in syphilis, but in tubercle they are one and all unreliable.

We are, indeed, greatly in need of a reliable serological test for tuberculosis. Nowadays new serum tests for this disease appear with conspicuous regularity only to be found wanting and relegated to the literature of the past. The sedimentation test appears to be the best of the non-specific ones, but I do not know how far it could be used as a means of differential diagnosis between syphilis and tuberculosis. I have refrained from discussing the tuberculin tests because I do not regard them as good tests of the activity of tuberculous disease; moreover, tuberculin at present is difficult to standardise with certainty.

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